

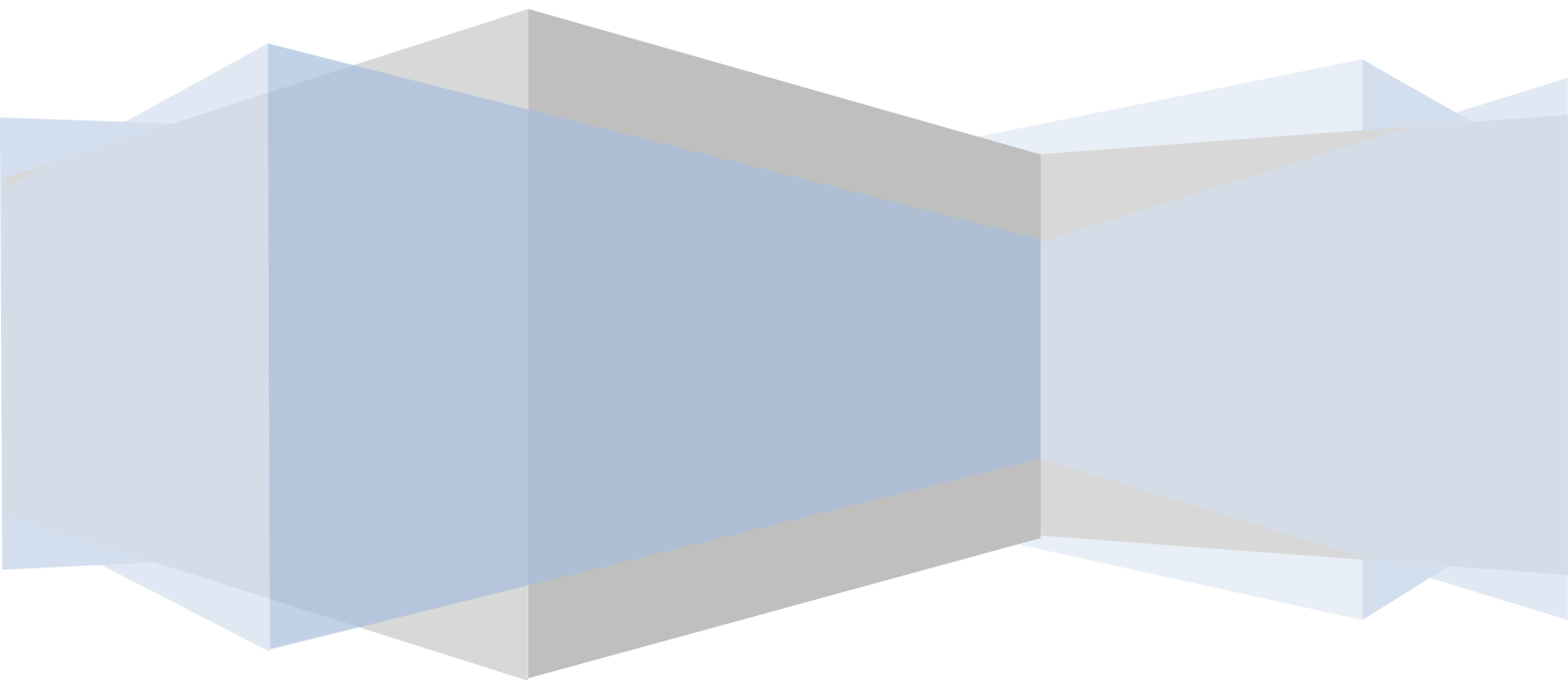
Faculty of Pharmacy



# **Introduction – part 2**

***Pharmacognosy & Phytochemistry***

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# Preparation of Drugs for the Commercial Market:

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## Factors affecting the development of the plant

- Many factors affect the development of the plants as well as their content of pharmacologically active compounds.
- Factors can be divided into two groups, **extrinsic ones**, such as **climate** and **soil**, and **intrinsic ones**, such as **genes**.

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## Intrinsic Factors:

- The improvement of the properties of cultivated plants can be achieved by 3 methods:

### ➤ Selection:

If a population of a plant has **not** been subjected to any genetic manipulation, it is generally composed of individuals with great variation in the genes which code for the property of interest.

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## Selection:

- **For example:** the content of a certain alkaloid. Thus some plants may have a **high**, other a **medium** content and some a very **low** content, i.e. **a variation in the content of alkaloids or a certain alkaloid coded by certain gene in the genetic makeup in the plant.**
- Selection aims to improve the yield of a desired compound, therefore a great number of plants are analyzed, and the ones with the **highest** content are propagated.
- Example: opium poppy, *Papaver somniferum*.

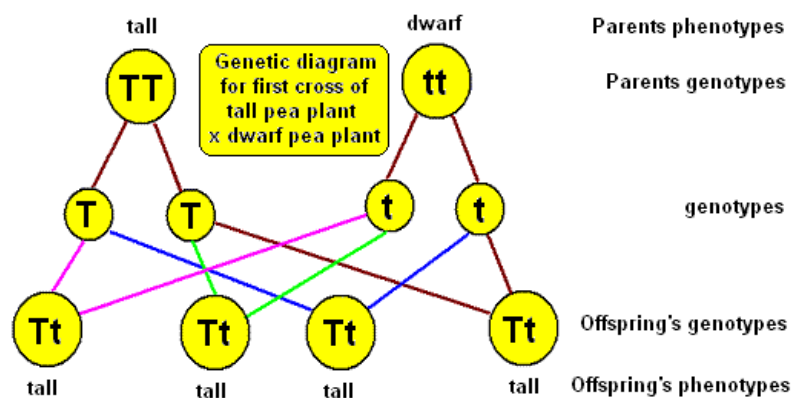
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## Cross-breeding التهجين

- ❖ This process is used largely in agriculture and production of the **ornamental plants**.
- ❖ Using cross-breeding is useful to obtain plants with interesting **morphological** or **biochemical** characters.
- ❖ Breeding of *Cinchona succirubra* with *Cinchona ledgeriana* yields a bark rich in alkaloids.
- ❖ Usually hybrids **have not stable characters**, and the next generation **will not retain** the properties.
- ❖ Propagation of hybrids **must** therefore be performed by vegetative reproduction (**such as propagation by vegetative organs like rhizomes and bulbs**).

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## Cross-breeding example:

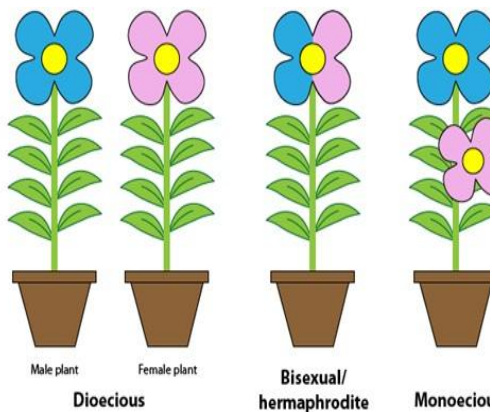


This offspring doesn't retain the desired characters unless propagated by vegetative reproduction.

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## Cross-breeding التهجين

- **Vegetative reproduction:** is a form of **asexual** reproduction in plants. It is a process by which new organisms arise without production of seeds or spores.



### Cross Breeding

- Combining two or more desirable features in ONE offspring.
- Example: Farmers wanted the tomato firm and square in shape.



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## Mutation:

- ❖ Constant alterations of genes which can be transferred to new generation of cell and plants are called mutation and can involve either DNA itself or the number of chromosomes in the plant.
- ❖ The mutation can occur **spontaneously** or **artificially** using e.g. **X** or **gamma** ray or **chemical agents**.
- ❖ Mutation can determine the losing of character/s or giving new character/s.
- ❖ *Belladonna* with the chromosome number **4n** produces larger amount of alkaloids than the original **2n**.

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## Chemical races and chemotypes

- Individuals of a population of plants which has not been subjected to genetic manipulation **التلاعب الجيني** may differ considerably in **the genes** which code for certain constituents, causing the plant to have a high or a low content of the constituent, **without differences in the morphological characters between these plants.**
- **Chemotype** is the same botanical species that has been modified or is occurring in other forms due to conditions of growth such as climate, soil or altitude. It is often referred to as **CT**.
- A **chemotype** (sometimes **chemovar**) is a chemically distinct entity in a [plant](#) or [microorganism](#), with differences in the composition of the **secondary metabolites**.

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## Chemotypes

- ❖ **Phenotype:** an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, phenology, behavior, and products of behavior (such as a bird's nest).
- ❖ Chemical properties in such a plant may vary from the original plant. **Examples of CT are:**
  - **Different chemotypes occur for the species *Thymus vulgaris*:**
  - **Thymol** and **carvacrol** types - these are warming and active oils.
  - **Thujanol** type - these are penetrating and antiviral oils.
  - **Alcohol** and **ester** types - non irritant and sweet smelling oils.

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## Collection of medicinal plants

- The task may be undertaken by casual, **unskilled** native labor or by **skilled** people
- **The season** is importance since the **amount** and sometimes the **nature** of the active constituents is not constant throughout the year.
- **For example:** **Rhubarb** **الراوند** contains no anthraquinone glycosides derivatives in **winter** but **anthranols** which on arrival of **warmer** weather, are converted by oxidation into anthraquinones.
- Anthranol-type glycosides are the reduced form of anthraquinones, and are more active.

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## Collection of medicinal plants

- ❖ The **age** of the plant is also important. There is increasing evidence that the composition of a number of secondary plant metabolites varies appreciably throughout the **day** and the **night**.
- ❖ The most advantageous time of collection is during that period when the plant part constituting the drug is highest in its content of active constituents.
- ❖ **Example of importance of the suitable time of harvesting** is ***Ephedra*** species, where the content of alkaloids is highly variable, and reaches the maximum in autumn.

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## Rules for collection

- These are general rules for collecting the parts of the plants rich in the active constituents. However, they DON'T apply for all plants.
  - Concentrate on the adverbial words and those that show the time exactly (e.g. after, before, at, late, ... etc.)
- **Roots and rhizomes:** are collected at the end of of the vegetation period (i.e. usually in **autumn**). In most cases, they must be washed free of adhering soil and sand.
  - **Bulbs:** late autumn, best after the plant has flowered and fruited.
  - **Bark:** in **autumn** after leaf fall, or **spring** before the development of the leaves. In spring, the cambium shows its maximum activity producing an abundance of undifferentiated cells that are still soft making stripping the bark, existing outside the cambium, easier. It is also approved to collect the bark after rain has fallen, as the bark will be damp and easy to be removed.

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## Rules for collection

- **Leaves and herbs:** at the flowering stage. It is preferred to collect the stems with the leaves, and separate them from each other later. Collection in the morning is important in some cases as with **Solanaceous** leaves.
- **Flowers:** usually when fully developed. Collection should be in **dry** weather and towards the middle of the day, after dew has dissipated. In certain cases, as with **cloves** (*Eugenia caryophyllata*), the unopen flower is picked.
- **Fruits and seeds:** when fully ripe and grown, or nearly grown.

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## Drying of medicinal plants

- Drying is the most common method for preserving plant material.
- Rapid removal of water guarantees enzymatic activity cessation, and hence, eliminating to a high extent the degradation of the active components.
- Also, it decreases the external attack, (e.g. by fungi).
- Generally, drying is done at relatively high temperatures to guarantee quick drying.
- **The chosen temperature should guarantee quick drying (whenever needed), and be suitable for a lot of components that are sensitive to heat.**

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## Drying of medicinal plants

- Many fresh drugs contain a considerable amount of water (60-90%), **and all moist drugs liable to develop mould, so they must be dried, as soon as possible.**
- **If enzyme action is to be encouraged, SLOW drying at a moderate temperature is necessary.**
- If enzyme action is **not** desired drying should take place **AS SOON AS** possible after collection.

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## Dry climate drying

- For **dry climates** arrangements drying may be carried out:
  1. Under the cover of sheds ,or
  2. At night, or
  3. We have sun-drying (when the active components are not adversely affected by drying in the sun).

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## Drying of medicinal plants

- Drying by **artificial** heat is more rapid than open air and is often necessary in **tropical** countries (where the **humidity** is very high).



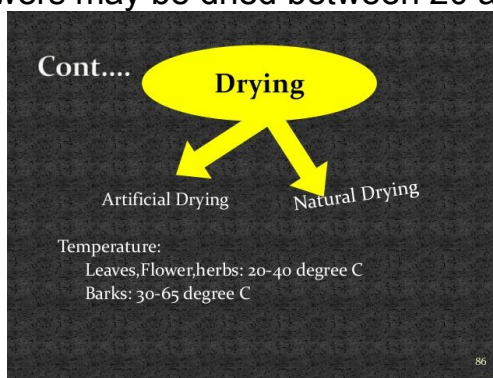
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## Drying of medicinal plants

- Fairly **rapid** drying helps **flowers** and **leaves** to retain their color and aroma.
- If leaves and other delicate structures are **over dried**, they become very brittle and tend to break.

### ❖ As a general rule:

1. Leaves, herbs, and flowers may be dried between 20 and 40 C.
2. Barks and roots between 30 and 65 C.



## Freeze drying

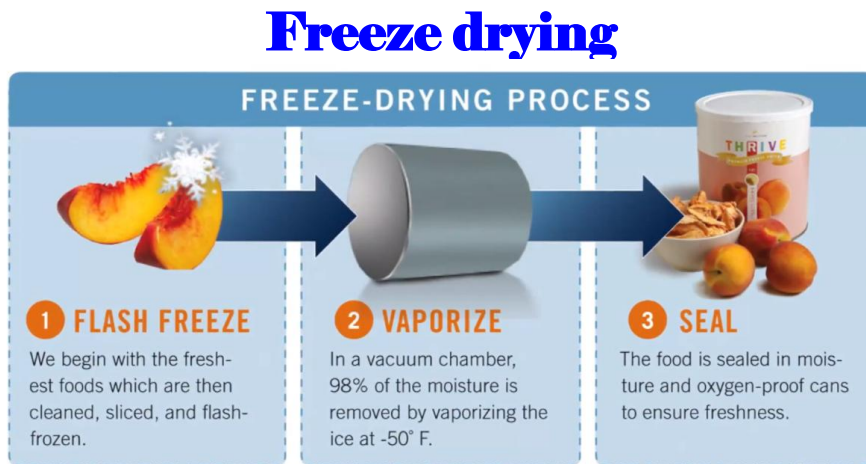
- **Freeze drying = Lyophilization:** is a very mild method of drying.
- Frozen material is placed in an evacuated apparatus which has a cold surface maintained **at -60 to -80 C**.
- Water vapour from the frozen material then passes rapidly to the cold surface.
- The method requires a relatively complicated apparatus and is much more expensive than hot-air drying.
- Lyophilization is very important for drying heat-sensitive substances, e.g. **antibiotics** and **proteins**.

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- ❖ Freeze-drying works by freezing the material and then **reducing** the surrounding pressure to allow the frozen water in the material to **sublimate** directly from the solid phase to the gas phase.

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## Stabilization

- Carried out by **denaturation** of the enzymes by treatment with heat.
- The most common method includes brief exposure (few minutes only) of the plant material to the ethanol vapour under pressure (0.5 atm).
- The operation is carried out in a *preheated* autoclave, so ethanol does not condense on the plant material.

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## Reasons for stabilization

- Drying implies delaying enzymatic reactions.
- If enzymes are left intact, they will start functioning again as soon as sufficient water is present.
- Moreover, considerable enzymatic degradation of the constituents may take place during the drying process.
- On long storage, enzymatic reactions will slowly destroy the constituents, because the last traces of water can never be removed.

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## Fermentation

- Enzymatic transformation of the original plant constituents is some time desirable.
- The **fresh** material is then placed in thick layers and exposed to raised **temperature** (30-40 C°) and **humidity**, so as to accelerate the enzymatic process.
- **This treatment is usually called fermentation**, the fermented product must be dried to prevent attack by microorganisms, e.g. moulds.
- **Fermentation is mostly used to:**
  1. Remove bitter or unpleasant-tasting substances, or
  2. Promote the formation of aromatic compounds with a pleasant smell or taste.  
Example: black tea and fermented vanilla.

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## Harvesting

- The mode of harvesting varies with the drug, some drugs may be collected by:
  1. **Hand labor**, or
  2. **Mechanical devices**. This method is more economic whenever it is possible.



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## Garbling

- Garbling is the final step in the preparation of a drug.
- It consists of the **removal of extraneous matter**, such as **other parts of the plant**, **dirt**, and **added adulterants**.
- This is done, to some extent, during collection but should be carried out after the drug is dried and before the drug is baled and packaged.
- The European pharmacopoeia requires that a crude drug contains no more than **2%** of foreign matter.



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## Garbling

- ❖ In **leaf** drugs (e.g. senna), an excess of stems must be removed.
- ❖ In some cases particles of iron must be removed with magnets.
- ❖ Dirt and sand can often be removed by **sifting** (sieving) or by means of **currents of air**.
- ❖ Sand in powdered plant may cause considerable damage to the dies and punches of the tablet machine.



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# Packaging

- ❖ The packaging of drugs is dependent upon their final disposition.
- ❖ Packaging should provide protection to the drug as well as give economy in space.
- ❖ Leaf and herb material is usually **baled** with power balers into a **solid compact mass**.
- ❖ For overseas shipment, such bales weigh from 100-250 pounds.



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## Preservation of drugs

- Proper storage and preservation are important.
- Warehouses preferably should be of **fire proof**, **unheated** and **rodent proof**
- Sacks and bales reabsorb about **10-12 %** or more of moisture.
- The **glycosides in digitalis** tend to deteriorate when moisture in the drug reaches **8%**.
- Oxygen of the air increases oxidation of the constituents of drugs.

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## Preservation of drugs

### ➤ Methods of prevention of insect attacks:

1. Exposure of the drugs to a temperature of **65 C°**.
2. The use of **methyl bromide** ( $\text{CH}_3\text{Br}$ ).
3. By the addition of few drops of **chloroform** ( $\text{CHCl}_3$ ) or **carbon tetrachloride** ( $\text{CCl}_4$ )

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## Preservation of drugs

- Replacement of air by **inert** gas is sometimes applied.
- Drugs, that likely deteriorate because of absorbed moisture (**e.g. digitalis**) are packed in **moisture-proof cans**.
- **Gums, resins** (substances produced by most plants e.g. cedar and pine, and are mainly composed of terpenes) and **extracts** are shipped in barrels and boxes.

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## DRUG ADULTERATION

- ❖ Adulteration, in the broad and legal sense is the debasement (cheating) of any article.
- ❖ It is the practise of substituitng a crude drug partially or whole with other similarly-looking substances which are either **free** from therapeutic properties or **inferior** in terms of chemical and therapeutic properties.
- ❖ **Inferior, spoiled or deteriorated** drugs represent the greatest percentage of cases of drug adulteration.<sup>77</sup>

## Admixture

**Admixture:** is the addition of one article to another through **accident, ignorance, or carelessness.**

- ❖ Accordingly, admixture is an **unintentional** (indeliberate) adulteration.
- ❖ Generally, **SOPHISTICATON** is the intentional or deliberate type of adulteration.
- ❖ Substitution may be either intentional or unintentional.<sup>78</sup>

## Sophistication

- The addition of an inferior material to any article which is **done intentionally to defraud**.
- : the addition of **wheat flour** to powdered **ginger**, with enough **capsicum** to restore or enhance the pungency (taste) and enough **curcuma** to maintain the color, would represent a typical example of sophistication (**true adulteration**).

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## Substitution

- Occurs when an **entirely different** article is used or sold in place of the one required.
- **Example:** cotton seed oil sold as olive oil.
- However, all types of substitution are considered legally as adulteration.



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# Deterioration

- Refers to the impairment of the **quality** of the drug during the process of preparation.

# Spoilage

- Refers to the deterioration fo the drug due to fungal or bacterial attack.

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# Inferiority

- **Inferiority** is a natural substandard condition (e.g. where a crop is taken whose natural constituent is below the minimum standard for that particular drug) which can be avoided by more careful selection of the plant material.

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